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THE RELATIONS BETWEEN NEUROSCIENCE AND HUMAN BEHAVIORAL SCIENCE

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Neuroscience seeks to understand how the human brain, perhaps the most complex electrochemical machine in the universe, works, in terms of molecules, membranes, cells and cell assemblies, development, plasticity, learning, memory, cognition, and behavior. The human behavioral sciences, in particular psychiatry and clinical psychology, deal with disorders of human behavior and mentation. The gap between neuroscience and the human behavioral sciences is still large. However, some major advances in neuroscience over the last two decades have diminished the span. This article reviews the major advances of neuroscience in six areas with relevance to the behavioral sciences: (a) evolution of the nervous system; (b) visualizing activity in the human brain; (c) plasticity of the cerebral cortex; (d) receptors, ion channels, and second/third messengers; (e) molecular genetic approaches; and (f) understanding integrative systems with networks and circadian clocks as examples.

Key words: neuroscience, brain, behavior-physiology relations, humans

There are major revolutions going on in neuroscience, and one can rightfully ask, do they have relevance for the study of human behavior and the traditional domains of psychiatry and psychology? Some of these revolutions are addressed below and show that considerable progress has been made in various aspects of neuroscience, ranging from the molecular to viewing the human brain during cognitive tasks. I am sure that there are some, perhaps many, clinical psychologists and psychiatrists who might feel that in the day-to-day practice of dealing with the real-life problems of patients, new information about brain mechanisms may not be immediately helpful. Although this attitude is understandable, and the challenge to understanding the human mind and behavior remains as great as ever, we must bear in mind that we could not have predicted in the early 1960s, at perhaps the peak of the Division of Neuropsychiatry at Walter Reed Army Institute of Research, how far we would get in comprehending the brain in just a few decades. This essay is in part a plea for the two fields of neuroscience and human behavioral science to keep communicating and in particular to encourage students who will bridge the gap.

Some Central Issues in the Human Behavioral Sciences

The central issues in psychiatry and clinical psychology are concerned with diagnosing and understanding the etiology of the disorders of thinking and overt behavior, particularly the serious disorders such as schizophrenia, bipolar affective disorder, and autism, and ideally generating remedies for these disorders. Perhaps the most unique aspect of humans is that we can be introspective. We are capable of examining our own thinking and feelings. It is not clear how much of human behavior is driven by conscious versus unconscious processes. It is likely that decision making always involves both processes in differing propor-

The Division of Neuropsychiatry at Walter Reed Army Institute of Research was unique in its time. One can say, without exaggeration, that it was the first Department of Neuroscience in the country in the 1960s. It had contained within its moderate physical space neuroanatomists, neurophysiologists, neuroendocrinologists, psychophysicists, experimental psychologists, psychiatrists and one of the earliest human sleep laboratories. Even today it would be hard to name a department in the country that has this much breadth in the neurosciences. The leadership within the Division of Neuropsychiatry was exceptional, particularly in terms of giving young people the opportunity to be creative. Unfortunately, in the current atmosphere of high biotech and the push for applications, the freedom of creativity is often compromised. We can continue to thank our past leaders such as the late David Rioch and Joe Brady, Bob Galambos, and Walle Nauta for those earlier wonderful opportunities. I was fortunate to have Bob Galambos as my supervisor from 1960 to 1962, when Bob went to Yale University, and then Joe Brady, until 1964. Joe and Bob, I miss the "good old days"; I thank you both for the truly positive experience.

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tions. We have no laboratory methodology at hand for measuring unconscious processes, although positron emission tomography (PET) and magnetic resonance imaging (MRI) may become useful in this area. It is because unconscious processes remain in the domain of psychiatry and clinical psychology, rather than experimental neuroscience, that it is perhaps the clearest divider of the two fields at the moment.

Clinical psychiatry and psychology often deal with the emotions and the "inner" lives of individuals, which are difficult subjects for experimental study. We know a good deal about how sensory input is processed in the brain, particularly visual stimuli (parallel processing of color, form, movement, etc.). However, we know little about the nature and processing of emotional information, except that the feelings generated by emotional pathways are more "diffuse." Such feelings are not localizable to external objects or body surfaces as in vision, audition, taste, and the tactile sense. It is quite interesting that parts of the human limbic system ("emotional brain") have grown in size, compared with chimpanzees, almost as much as our neocortex (see below).

The central issues in neuroscience concern how neurons and their supporting cells, the glia, are developed and work interactively to produce the integrative actions of the nervous system, a system that interacts with and adapts to the environment. Neuroscience is interested in human thinking and feeling, but it tends to take a reductionist approach in all of its central problems. It is a legitimate question to ask if the reductionist approach is helpful in understanding these activities. No attempt to answer this question is provided in this article. Rather, examples are given of current approaches to understanding nervous systems that are likely to have relevance for the human behavioral sciences. At least six revolutions in neuroscience, with relevance for the behavioral sciences, have occurred, and these are discussed below.

Revolution 1: Evolution of the Nervous System

The differences between a chimpanzee and a human, in terms of DNA, are about 1.6% (Sibley, Comstock, & Ahlquist, 1990). That 1.6% difference must account for all the special attributes of humans, of which speech and language stand out. Even so, there is clear evidence that chimpanzees demonstrate "conversational competence" (e.g., Greenfield & Savage-Rumbaugh, 1993). By repetition of a learned symbol system, chimpanzees can participate in conversation exhibiting agreement, request, promise, excitement, and selection from alternatives.

Neurons are surprisingly conservative, from an evolutionary point of view (Strumwasser, 1973). The electrical signaling mechanisms within a single neuron depend on both the passive cable properties of dendrites and axons and the amplification due to ion flow down electrochemical gradients. Such ion flow occurs through protein channels in the surface membrane. This form of conduction (signaling) within a single neuron remains unchanged from cnidarians (coelenterates), in which nerve cells first appeared, to humans. Furthermore, throughout the evolutionary scale, synaptic transmission between neurons or between neurons and effectors depends primarily on release of transmitters. Universally, these small transmitter molecules bind to protein receptors on the postsynaptic cell.

Important transmitters in the mammalian brain, such as acetylcholine, dopamine, serotonin, γ-amino butyric acid (GABA), and glycine, are all operative in "lower" animals. As one example, serotonin, thought to play an important role in human depression, is a potent modulatory transmitter in mollusks, acting in a variety of physiological processes involved in activities such as feeding, learning, and circadian rhythms. One of the serotonin receptors has been cloned in the freshwater mollusk *Lymnaea stagnalis* from genomic DNA (Sugamori et al., 1993). GABA also plays an important role in generating inhibition in the mammalian brain as well as in the round worm *Caenorhabditis elegans,* which has been intensely studied with molecular genetic approaches (McIntire, Jorgensen, & Horvitz, 1993). Peptide neurotransmission is found in mammals as well as in the lower animals. In mollusks a neuropeptide ("egg-laying hormone") acts to release eggs from the gonad as well as on central neurons that control behavior (Strumwasser, 1988). In rats, when the synthesis of neuropeptide Y receptors in the cerebral cortex is blocked, by using antisense oligodeoxynucleotides injected into the lateral cerebral ventricles, they exhibit more signs of anxiety in a behavioral task (Wahlestedt, Pich,

Koob, Yee, & Heilig, 1993). Thus, neuropeptide Y may be an important transmitter in controlling the emotion of anxiety in mammals.

What appears to have changed most in the evolution of the nervous system is the richness of detail in evaluating the world around us, and as a consequence adapting to and manipulating the external world. Often the number of neurons dedicated to a particular task may seem trivial or inappropriately small, such as the few tens of thousands of primary hair cells in the inner ear with which sound waves are transduced into impulses, or when nine neurons run the beat of the lobster heart. At the other extreme the human neocortex contains billions of cells involved in parallel processing of various sorts. Yet, for the important aminergic modulatory systems of the mammalian brain, such as the locus ceruleus (norepinephrine), raphe nuclei of the pons (serotonin), substantia nigra, and ventral tegmental area (dopamine), the numbers of cells are small (about 5,000 for norepinephrine and 20,000 for dopamine). However, these small numbers of cells can alter the balance of cerebral processes sufficiently to cause severe mood changes (such as depression and mania) and to cause hallucinations and delusions, as judged by the positive impact of specific psychotropic drugs that bind to the amine receptors.

If one examines the volumes of different structures in the mammalian brain and normalizes the volumes to the surface area (or exponent of the body mass) of the species, certain trends emerge, and there are some surprises. The human neocortex has increased in volume by a factor of about 3.2 relative to the pongid apes. However the septum and amygdala, parts of the limbic system, have increased a factor of 2.5 and 2.4, just lagging behind the neocortex (Table 1). Thus, it appears that our "emotional" brain more or less increased in size along with the neocortex. One can argue that increases in processing the emotions associated with object recognition must have had real survival value during the course of evolution. Emotions can be considered "anticipatory" in nature. Hearing a growl in a dark forest means "danger," or viewing the scowl on a human face could imply anger or nonacceptance. There is new information on where such emotional interpretations may be taking place in the brain. It is of relevance that bilateral destruction of the amygdala in rats produces a "fearless" rat that will even attempt to nibble on a sleeping cat's ears (Barinaga, 1992). It is thought that the amygdala may "be involved in the modulation of sensory processing by affective states," and that it is associated "with stimulus identification rather than location" (Aggleton, 1993, p. 329).

Table 1

Ratio of size indices of human to pongid brain components. These ratios were obtained by computing a ratio of columns 6 to 5 from Table 3.1 in Eccles (1989). The data in Eccles's table come from Stephan, Baron, and Frahm (1988) cited as a personal communication.

Neocortex	3.17
Septum	2.52
Cerebellum	2.46
Amygdala	2.42
Corpus striatum	1.87
Mesencephalon	1.80
Diencephalon	1.72
Hippocampus	1.63
Medulla oblongata	1.30

Revolution 2: Visualizing Activity in the Human Brain

This is an area in which PET and MRI are causing a revolution in neuroscience (see Gilman, 1992; Na, Doraiswamy, Lee, & Krishnan, 1991). It is now possible with PET to measure the selective distribution of very energetic radioactive compounds, ones that emit positrons, in the brain. With PET one can measure regional blood flow in the brain, which is proportional to neuronal activity, using O^{15}. Alternatively, one can measure glucose consumption by a number of radioisotopes including 2-[F^{18}]fluoro-2-deoxy-D-glucose. It is possible to demonstrate that seeing a word, hearing a word, or speaking will light up different areas of the brain (occipital lobe for vision, superior temporal lobe for audition, and Wernicke's speech area for speech). Also, with PET one can measure the binding of radioligands to different receptors. Currently, radio-ligands are available for PET work on a variety of brain receptors—the dopamine, opiate, benzodiazepine, and cholinergic receptors.

A number of studies have been made already, using PET, of patients diagnosed with schizophrenia and depression. There are some results and disputes of interpretation. The most general result in schizophrenics is the presence

of a decreased anterposterior metabolic gradient, or *cerebral hypofrontality* (reviewed in Bachneff, 1991; Baxter et al., 1991). The dorsolateral prefrontal cortex is implicated in another study on schizophrenic subjects (Friston, 1992). Other reports show findings of high blood flow in the left globus pallidus and steeper subcortical to cortical gradient in patients versus controls. It is thought that "hyperfrontality and hypofrontality could be a consequence and not a cause of positive and negative symptoms, respectively" (Bachneff, 1991, p. 860).

Changes in cerebral blood flow, resulting from cellular activity in the brain, can be measured by MRI through the paramagnetic effects of venous deoxyhemoglobin on water protons (Ogawa et al., 1993). The advantages of MRI over PET, as far as activity-dependent changes in cerebral hemodynamics are concerned, are better resolution (1 mm^3), no requirement for use of radioisotopes, and speed.

Most recently, rapid MRI has loomed as an astonishing method with which to follow some of the dynamics in brain during thinking (Kwong et al., 1992; Shulman, Blamire, Rothman, & McCarthy, 1993). Echo-planar imaging (EPI) can resolve brain images in the range of 40 to 128 ms during cognitive tasks. It has been possible, using standard MRI, to detect anatomical reductions in brain structures such as the left posterior superior temporal gyrus and mid corpus callosum in a schizophrenic population (McCarley et al., 1993; Woodruff, Pearlson, Geer, Barta, & Chilcoat, 1993). The application of rapid MRI to cognition might provide more information on the extent to which brain reaction to events in the external world differs in schizophrenics and control subjects.

Revolution 3: Plasticity of the Cerebral Cortex

The sensory cerebral cortex was thought of, for a long time, as a hard-wired machine for analyzing the outside world. It was certainly never thought of as a *tabula rasa,* at least by neurophysiologists in modern times. The early experiments of Hubel and Wiesel on the impact of monocular deprivation or strabysmus in the kitten on the subsequent properties of visual cortical neurons demonstrated that there was a fair amount of plasticity. However, over the last few years, even the structural plasticity has been shown to be surprisingly large. There is a large reduction in the axonal arbors of lateral geniculate neurons projecting to Layer 4 after just 7 days of monocular deprivation (Antonini & Stryker, 1993).

If a digit on the hand of an adult owl monkey is amputated, the area of the sensory cortex representing the neighboring digits expands into the territory of the amputated digit (Merzenich et al., 1984). In addition, there is a magnification of the skin area in the adjoining digits, with a corresponding decrease of the receptive tactile fields. In other words, the cortical maps of the adjoining digits developed a finer grain to them for analysis of the external world.

Another more recent study of the visual cortex shows that laser lesions in a focal area of the retina will immediately cause large (fivefold) expansions of the receptive field of the neighboring retina in the primary visual cortex of the adult monkey (Gilbert & Wiesel, 1992). The major conclusion from these and other studies is that cortical representation of the sensory world is dynamically maintained even in the adult.

Walsh and Cepko (1992, 1993) have examined the development of the rat neocortex by some very creative molecular biological techniques. They found that a single progenitor cell can give rise to unclustered neuronal clones in very different locations of the cortex (e.g., visual, somatosensory, and motor). These authors conclude "that cortical neurons are not specified regarding their ultimate areal fate by a lineage-based mechanism. Functional specification must arise through mechanisms acting after neurogenesis" (1992, p. 438). It is likely that neural activity in sensory pathways plays an important role in shaping cortical neurons after neurogenesis.

The human cerebral cortex is considered to be the highest evolutionary level of any nervous system. Presumably, the results of dynamic maintenance of cortical boundaries (and receptive fields) for monkeys and cats have parallels in humans. Also, the fact that specification of individual cortical cells, for a specific function, is not determined during neurogenesis in the rat suggests that the cortex probably tunes in to the external world for many of its controlling cues during maturation. This simply emphasizes the importance of early experience in cortical development and gives what psychiatrists and clinical psychologists already appreciate in humans a firmer biological basis.

One should add that the older parts of the mammalian brain (e.g., hindbrain) may develop by much more rigid mechanisms (i.e., lineage-dependent mechanisms); however, much remains to be determined about their development. It might be suspected, because these areas play a role in vegetative and emotional functions in mammals, that the development of these areas are less dependent on early experience and hence are more rigidly hard-wired. Also, we need to know more about the development of the limbic system and whether there is a dynamic maintenance of emotional mapping in the adult, as has been found in the neocortex for sensory representation.

Revolution 4: Receptors, Ion Channels and Second/Third Messengers

Perhaps knowledge in this area can be said to have expanded faster than any of the other areas of neuroscience over the last decade. Two themes have emerged. First, there is now structural information about many ion channels and receptors that was not available a mere decade ago. The second theme is the clearer understanding of how modulation and long-lasting changes in the nervous system come about. Enormous insights in the role of second and now third messengers, as well as protein phosphorylation, in generating modulation and long-lasting changes in neurons have arisen in the last decade.

The first virtually complete primary structure of any membrane protein was that obtained on the nicotinic cholinergic receptor of the electrocytes of the electric fish *Torpedo,* using cDNA technology, by Numa (Noda et al., 1983). No longer does one have to purify a membrane protein if it is a member of a family of membrane ion channels or proteins. An oligonucleotide probe, coding for a portion of the protein of one member of the family, can be used to screen a cDNA library, or, using the polymerase chain reaction, a specific messenger RNA can be amplified; in this way, nucleotide sequence can eventually be obtained on other members of the family. The technology is so powerful that it can produce papers that talk about having cloned several *thousand* human brain genes (Adams et al., 1992)!

The major ion channels (for Na^+, K^+, Ca^{2+} and Cl^-) have been cloned and sequenced (Hille, 1992; Jan & Jan, 1992). Receptors cloned include the dopamine (DA) and serotonin receptors, which have great relevance for psychiatry. Receptors exist as families with small but important differences between them. For example there are at least five related DA receptors, not counting alternatively spliced forms and pseudogenes. The rat D_2 dopamine receptor, implicated in the pathophysiology of schizophrenia, was the first to be cloned (Bunzow et al., 1988). The homologue of the human gene for the D_{1B} dopamine receptor has been localized to the short arm of Chromosome 4 (4p16.3), the same region as the Huntington disease gene (Tiberi et al., 1991). Even the cocaine-sensitive dopamine reuptake transporter has been cloned recently (Usdin, Mezey, Chen, Brownstein, & Hoffman, 1991). A similar situation exists for the serotonin receptor, in that it is a family of receptor subtypes, many of which have been cloned, including the serotonin transporter. The specificity of receptor subtypes can be appreciated by a recent study that shows that a highly specific agonist of the D_3 receptor, which is distributed primarily in the limbic projections of the mesocorticolimbic system, potently decreases self-administration of cocaine in rats (Caine & Koob, 1993).

Modulation. A short time ago, it was thought that transmitter ligands only directly operated ion channels. This pervasive attitude was based on a great deal of knowledge, gained over the years, about the nicotinic acetylcholine (ACh) receptor at the neuromuscular junction. We now know that this receptor is more the exception than the rule. There has been a real revolution in the understanding of signal transduction in neurons, endocrine, and other cells, all stimulated by the work of Sutherland and Rall (1957), who discovered that adenosine 3′,5′ cyclic monophosphate (cAMP) mediates the action of the hormone epinephrine on liver glycogenolysis. For many neurons, transmitter receptors are coupled to second messenger enzymes through guanine-nucleotide-binding proteins that generate the intracellular messengers such as cAMP. The importance of second messengers is that they cause prolonged intracellular and membrane actions that far outlast the presence of the neurotransmitter in the synaptic cleft.

Work on the afterdischarge of the neuroendocrine bag cells of the mollusk *Aplysia* has been particularly instructive as to how long-lasting changes in membrane properties are

brought about by only brief synaptic input (Strumwasser, 1988). We asked the question as to whether isolated bag cells, which ordinarily are quiescent, could produce long-lasting discharges in the absence of synaptic input. About 20 min after adding a permeable form of cAMP to the culture medium, spontaneous activity starts in isolated bag cells. What is very impressive is that in the presence of cAMP, a regular afterdischarge is initiated by a brief depolarization that elicits Ca^{2+}-mediated spikes. The lesson is that a long-lasting program of membrane activity can be initiated by the combination of two messengers, cAMP and Ca^{2+}.

The relevance for the human behavioral sciences is that most psychoactive drugs presently either block specific pre- or postsynaptic amine receptors or interfere with the reuptake mechanism of the transmitter in the presynaptic terminal. As more subtypes of receptors are discovered by cloning and expression techniques, more specific drugs can be designed and tested. Receptor regulation studies show that up- and down-regulation of receptors occur, and these phenomena depend on phosphorylation mechanisms (and other posttranslational modifications) as well as gene regulation (transcriptional mechanisms). I think that it is fair to say that the long latency of some psychoactive drugs (e.g., the antidepressant imipramine) suggests that the initial action (e.g., blocking reuptake to prolong transmitter action) is only the first step in a long chain of events that involves up- or down-regulation of autoreceptors and postsynaptic receptors and leads ultimately to alterations in the balance of second and third messenger systems (e.g., transcription regulators). A start in this area has been made by the work of Merchant and Dorsa (1993), who showed that there is an increase in messenger ribonucleic acid (mRNA) coding for the antipsychotic-like peptide neurotensin in the nucleus accumbens after treatment with antipsychotic drugs such as haloperidol or clozapine. It is possible that PET and MRI studies in humans will help sort out some of these long-term steps.

Revolution 5: Molecular Genetic Approaches

There has been a revolution in determining the genes and their defects in nonpsychiatric illnesses. The human genome contains about 100,000 genes; it is thought that about 30,000 of these genes are expressed specifically in the nervous system (Breakefield, 1992). At present the number of known neurological mutations are about 30. The gene defect for Huntington's chorea has been determined (The Huntington's Disease Collaborative Research Group, 1993). It is a trinucleotide ("triplet") repeat that is expanded and unstable on Chromosome 4 (locus 4p16.3). Other examples in the medical field include the cystic fibrosis gene defect, which turns out to be a chloride channel flaw, and the Duchenne muscular dystrophy gene defect, which is due to an error in a muscle structural protein associated with the plasma membrane. There have been some false starts in determining gene errors related to schizophrenia and bipolar affective disorder, but it is likely that they will eventually come to light.

There is current speculation that genes with triplet repeats (as in Huntington's chorea) are candidates for mediating some neuropsychiatric disorders in which there is an unusual pattern of inheritance demonstrating *genetic anticipation* (Ross, McInnis, Margolis, & Li, 1993). Genetic anticipation refers to the fact that in successive generations, the severity of the disorder increases and the age of onset decreases, as in spinocerebellar ataxia type I (Davies, 1993). It is thought that bipolar affective disorder and certain forms of schizophrenia may be candidates for genetic anomalies involving triplet repeats (Ross et al., 1993).

Transgenic approaches. The fact that foreign genes can be inserted into the fertilized egg or preblastula embryo, allowing these genes to be expressed in the transgenic animal, shows great promise as a research tool. One of the earliest demonstrations of the power of the transgenic approach came from the field of endocrinology, where investigators inserted Growth hormone (GH) genes in mice with a metallothionein promoter. Whenever the mice drank water doped with a heavy metal, the metallothionein promoter was activated and GH transcripts were produced, causing these mice to grow much larger than their controls (Palmiter, Norstedt, Gelinas, Hammer, & Brinster, 1983).

The relevance for the human behavioral sciences of transgenic approaches is as a research tool with laboratory animals. Recently, transgenic approaches involving mutating or deleting specific genes have been used to interfere with learning and memory mechanisms in the

brain. Mice with a dysfunctional -Ca^{2+}-calmodulin dependent kinase II gene are impaired in spatial learning (Silva, Paylor, Wehner, & Tonegawa, 1992). This kinase is enriched in the postsynaptic densities of the hippocampus and neocortex. Furthermore, long-term potentiation in the hippocampus is impaired in these mutant mice (Silva, Stevens, Tonegawa, & Wang, 1992). Similar findings have been described when defects are produced in one of four tyrosine kinase genes (*fyn*) by using transgenic mice (Grant et al., 1992). Eventually, the use of the transgenic approach should allow eliminating the dopaminergic system (or other modulatory systems) in highly selective ways (nigro-striatal vs. meso-limbic) and using these mice in behavioral and pharmacological studies. The technique of specific cell immortalization should allow production of an endless supply (i.e., a cell line) of mammalian dopaminergic or serotonergic neurons that can be studied physiologically or neurochemically in a dish.

Revolution 6: Understanding Integrative Systems: Networks and Circadian Clocks As Examples

When the task of defining the important molecules of the nervous system is finished, we will still have to explain behavior in terms of networks and the specialized properties of certain neurons. Integrative processes in the nervous system depend on the precise nature of interneuronal connections and the individual properties of the cells in the population. There are promising preparations available for beginning to understand how the assemblies of neurons in a nervous system are able to produce coordinated behavior.

Networks. In the mammalian brain, it is very difficult to study the interaction of specific neurons in a circuit because of problems of visualization, mechanical stability, and accessibility. Nevertheless, using chronic unit recording techniques (Strumwasser, 1958), it has been possible to record from about 100 neurons simultaneously in the hippocampus of the behaving rat and confirm that the pyramidal cells code for the location of objects in space (Wilson & McNaughton, 1993).

Because the evolution of the nervous system is conservative, we can learn much about systems of neurons from lower animals in which neurons are more accessible. In the abdominal ganglion of *Aplysia,* it has been possible to record from hundreds of neurons simultaneously (about 50% of the total neuronal population of about 700 neurons), over a few hours, during reflex stimulation, using membrane-potential sensitive dyes (Wu et al., in press). Although the ganglion is isolated, it is still connected to a source of sensory afferents, the siphon, and to a motor output, the gill. One of the surprising results in this study was the large number of neurons that receive afferent input from the siphon, only one of several possible sources of afferents. One interpretation of the wide divergence of sensory afferents in the abdominal ganglion is that it allows each animal to prune these afferent inputs with experience. The interanimal variance that Wu et al. describe might reflect very different interactions of these organisms with their environments.

Clocks. Behavior has periodic components in breathing, sleeping, waking, eating, drinking, social activity, migrating, and hibernating. In each of us, every day, there is a temporal program of neural and endocrine activity that can be said to organize our metabolic, sensory, motor, and emotional activities across 24 hr. In the last decade or two, we have learned a considerable amount concerning how these internal programs are organized and where they are located. The stages of wakefulness, sleep, and endocrine rhythms in humans over the course of 24 hr have been well worked out since the pioneering experiments of Aschoff and colleagues in studying humans over long periods in total isolation from normal environmental cues (Moore-Ede, Sulzman, & Fuller, 1982). Growth hormone is released during the first slow-wave sleep of the night. Cortisol secretion starts to rise before arousal. The phase relationships of various hormone secretions and metabolic activities are very precise for any one human and represent an interesting fingerprint of the internal temporal organization of that human's body clocks. Although internal body clocks are entrained primarily by the light/dark cycle, they free-run under constant conditions of either constant light or darkness. In other words, the cycle of activity is due to an internal neuronal mechanism that varies systematically with time.

Perhaps the most dramatic alteration of the internal clock occurs in manic-depressive illness (Wehr, Sack, Rosenthal, Duncan, & Gil-

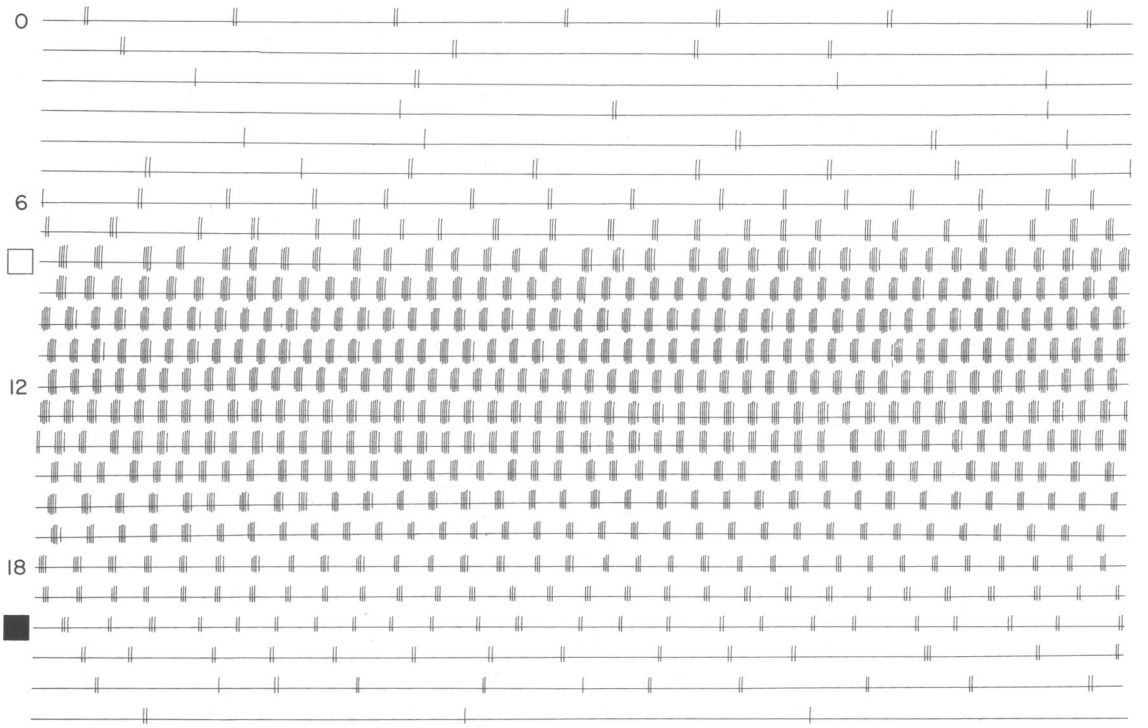

Fig. 1. Continuous recording of compound action potential (CAP) electrical activity from an isolated eye of *Aplysia californica* for the first 24 hr. The recording was obtained by a suction electrode on the optic nerve. Each vertical pulse is a CAP emitted by the synchronized discharge of the neurosecretory cells into the optic nerve. The eye had been dissected several hours before the record shown and was maintained in darkness and at a constant temperature (14 °C) throughout the recording. Each line is 1 hr long; the first line begins at midnight. The intact animal had been exposed to a light/dark cycle whose onsets are illustrated by the open and filled squares, respectively; projected light on at 8:00 a.m. and light off at 8:00 p.m. (from Strumwasser, 1987).

lin, 1983). In this study, subjects were tracked for several cycles of manic depression with periods greater than a month, measuring body temperature, electroencephalogram sleep, and a self-rating of mood. There is little doubt from these and other data that the phases of particular circadian variables are strongly correlated with mood.

Manic-depressive illness can be understood as a circadian disorder in the following way. "Beats" originate when two oscillations (e.g., tones), close in frequency, are simultaneously produced. A half-hour difference in period each day between two circadian oscillations that cannot mutually entrain each other will give rise to a beat period of about 48 days (see Halberg, 1960). Richter (1965) has provided many clinical examples of cyclical illnesses that have periods ranging from 7 days to 10 years.

Where is the timing mechanism located? The suprachiasmatic nuclei (SCN) of the hypothalamus are the seat of the major circadian oscillator system in mammals. They are small structures, consisting of about 5,000 to 10,000 neurons on each side of the brain. When the SCN are totally destroyed, free-running circadian activity is no longer observed in rodents and monkeys. In addition there is direct evidence from the brain-slice studies of Green and Gillette (1982) of a circadian oscillation of spontaneous impulse rate in the SCN.

The pineal gland in certain birds appears to drive the circadian rhythm of locomotor activity. Pinealectomy produces a total desynchronization of the sleep–wake cycle in a sparrow (Gaston & Menaker, 1968); the cycle can be restored by transplantation of the pineal gland into the anterior chamber of the eye. The pineal gland of donor birds on a reversed light/dark schedule, when transplanted into pinealectomized birds, will generate a sleep–wake cycle that is in phase with the donor

(Zimmerman & Menaker, 1979). These remarkable findings mean that a small piece of neuroendocrine tissue drives the circadian behavior of an entire organism. Similar experiments have been done in mammals using SCN grafts placed in the third ventricle in the brain of rats and hamsters with bilateral SCN lesions (Ralph, Foster, Davis, & Menaker, 1990; Ralph & Lehman, 1991). Rhythmicity is restored with the period of the donor. Because very few fibers enter the host tissue from the graft, this suggests that humoral communication is likely (Canbeyli, Lehman, & Silver, 1991).

Can we observe the "ticking" of the circadian clock? We have worked with a circadian oscillator in the eye of a marine mollusk that controls the rest/activity cycle of the whole organism (reviewed in Koumenis & Eskin, 1992; Strumwasser, 1987; Strumwasser & Vogel, 1992). Figure 1 illustrates 1 day in the electrical life of this totally isolated eye maintained in darkness. The isolated eye begins to "wake up" between 5 and 6 a.m., some 2 hr before the old light/dark schedule would have been applied to the intact animal. Maximum activity occurs around projected dawn. Right and left eyes from the same organism, but isolated from each other, virtually superimpose their circadian activities.

We described the circadian aspects of a manic-depressive cycle above. Lithium (Li^+) is one of the most effective treatments for bipolar affective disorder. Also, Li^+ turns out to be most effective at increasing the period of the circadian rhythm in a dose-dependent manner in the isolated eye of *Aplysia* (Figure 2, from Wollum & Strumwasser, 1983). Therefore, it appears likely that one of the actions of Li^+ in humans is to lengthen the circadian period. We also find that caffeine and lanthanum have the same effects. All of the above agents are pharmacologically able to increase Ca^{2+} levels in cells.

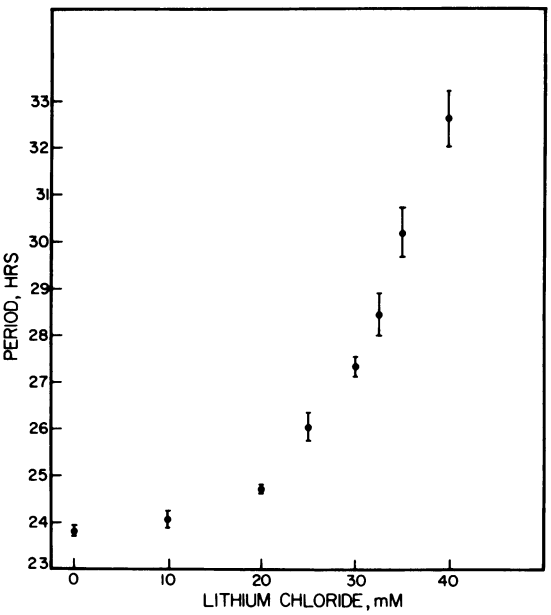

Fig. 2. Dependence of the mean period of the circadian rhythm of CAP activity in the eye of *Aplysia californica* on external Li^+ concentration. Error bars are *SEM* (from Wollum & Strumwasser, 1983; see text of this paper for further details).

Conclusion

Psychiatry and clinical psychology deal with disorders of human behavior and mentation. Neuroscience seeks to understand how the human brain, perhaps the most complex electrochemical machine in the universe, works, in terms of molecules, membranes, cell assemblies, development, plasticity, learning, memory, cognition, and behavior. That is a tall order. We are not there as yet, but we have come a long way in just three or four decades. Our students and their students will help to bridge the gap between the two fields.

REFERENCES

Adams, M. D., Dubnick, M., Kerlavage, A. R., Moreno, R., Kelley, J. M., Utterback, T. R., Nagle, J. W., Fields, C., & Venter, J. C. (1992). Sequence identification of 2,375 human brain genes. *Nature, 355,* 632–634.

Aggleton, J. P. (1993). The contribution of the amygdala to normal and abnormal emotional states. *Trends in Neurosciences, 16,* 328–333.

Antonini, A., & Stryker, M. P. (1993). Rapid remodeling of axonal arbors in the visual cortex. *Science, 260,* 1819–1821.

Bachneff, S. A. (1991). Positron emission tomography and magnetic resonance imaging: A review and a local circuit neurons hypo(dys)function hypothesis of schizophrenia. *Biological Psychiatry, 30,* 857–886.

Barinaga, M. (1992). How scary things get that way. *Science, 258,* 887–888.

Baxter, L. R., Guze, B. H., Schwartz, J. M., Phelps, M. E., Mazziotta, J. C., & Szuba, M. P. (1991). PET studies of cerebral function in major depression and related disorders. In N. A. Lassen, D. H. Ingvar, M. E. Raichle, & L. Friberg (Eds.), *Brain work and mental activity* (pp. 403–418). Copenhagen: Munksgaard.

Breakefield, X. O. (1992). Molecular approaches to diseases of the nervous system. In Z. W. Hall (Ed.), *An introduction to molecular neurobiology* (pp. 496–530). Sunderland, MA: Sinauer.

Bunzow, J. R., Van Tol, H. H. M., Grandy, D. K., Albert, P., Salon, J., Christie, M., Machida, C. A., Neve, K. A., & Civelli, O. (1988). Cloning and expression of a rat D2 dopamine receptor cDNA. *Nature, 336,* 783–787.

Caine, S. B., & Koob, G. F. (1993). Modulation of cocaine self-administration in the rat through D-3 dopamine receptors. *Science, 260,* 1814–1816.

Canbeyli, R. S., Lehman, M., & Silver, R. (1991). Tracing SCN graft efferents with DiI. *Brain Research, 554,* 15–21.

Davies, K. (1993). Triplet repeats on the rise. *Nature, 364,* 88.

Eccles, J. C. (1989). *Evolution of the brain: Creation of the self.* London: Routledge.

Friston, K. J. (1992). The dorsolateral prefrontal cortex, schizophrenia and PET. *Journal of Neural Transmission, 37*(Suppl.), 79–93.

Gaston, S., & Menaker, M. (1968). Pineal function: The biological clock in the sparrow? *Science, 160,* 1125–1127.

Gilbert, C. D., & Wiesel, T. N. (1992). Receptive field dynamics in adult primary visual cortex. *Nature, 356,* 150–152.

Gilman, S. (1992). Advances in neurology. *New England Journal of Medicine, 326,* 1608–1616.

Grant, S. G. N., O'Dell, T. J., Karl, K. A., Stein, P. L., Soriano, P., & Kandel, E. (1992). Impaired long-term potentiation, spatial learning, and hippocampal development in *fyn* mutant mice. *Science, 258,* 1903–1910.

Green, D. J., & Gillette, M. U. (1982). Circadian rhythm of firing rate recorded from single cells in the rat suprachiasmatic slice. *Brain Research, 245,* 198–200.

Greenfield, P. M., & Savage-Rumbaugh, E. S. (1993). Comparing communicative competence in child and chimp: The pragmatics of repetition. *Journal of Child Language, 20,* 1–26.

Halberg, F. (1960). Temporal coordination of physiologic function. In *Biological clocks. Cold Spring Harbor Symposia on Quantitative Biology, 25,* 289–310.

Hille, B. (1992). *Ionic channels of excitable membranes.* Sunderland, MA: Sinauer.

The Huntington's Disease Collaborative Research Group. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell, 72,* 971–983.

Jan, L. Y., & Jan, Y. N. (1992). Structural elements involved in specific K^+ channel functions. *Annual Review of Physiology, 54,* 537–555.

Koumenis, C., & Eskin, A. (1992). The hunt for mechanisms of circadian timing in the eye of *Aplysia. Chronobiology International, 9,* 201–221.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., Turner, R., Cheng, H.-M., Brady, T. J., & Rosen, B. R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences, U.S.A., 89,* 5675–5679.

McCarley, R. W., Shenton, M. E., O'Donnell, B. F., Faux, S. F., Kikinis, R., Nestor, P. G., & Jolesz, F. A. (1993). Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. *Archives of General Psychiatry, 50,* 190–197.

McIntire, S. L., Jorgensen, E., & Horvitz, H. R. (1993). Genes required for GABA function in *Caenorhabditis elegans. Nature, 364,* 334–337.

Merchant, K. M., & Dorsa, D. M. (1993). Differential induction of neurotensin and *c-fos* gene expression by typical versus atypical antipsychotics. *Proceedings of the National Academy of Sciences, U.S.A., 90,* 3447–3451.

Merzenich, M. M., Nelson, R. J., Stryker, M. P., Cynader, M. S., Schoppmann, A., & Zook, J. M. (1984). Somatosensory cortical map changes following digit amputation in adult monkeys. *Journal of Comparative Neurology, 224,* 591–605.

Moore-Ede, M. C., Sulzman, F. M., & Fuller, C. A. (1982). *The clocks that time us.* Cambridge, MA: Harvard University Press.

Na, C., Doraiswamy, P. M., Lee, K. H., & Krishnan, K. R. (1991). Magnetic resonance imaging in biological psychiatry. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 15,* 581–593.

Noda, M., Takahashi, H., Tanabe, T., Toyosato, M., Kikyotani, S., Furutani, Y., Hirose, T., Takashima, H., Kiyano, T., Inayama, S., Miyata, T., & Numa, S. (1983). Structural homology of *Torpedo californica* acetylcholine receptor subunits. *Nature, 302,* 528–532.

Ogawa, S., Menon, R. S., Tank, D. W., Kim, S. G., Merkle, H., Ellermann, J. M., & Ugurbil, K. (1993). Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophysical Journal, 64,* 803–812.

Palmiter, R. D., Norstedt, G., Gelinas, R. E., Hammer, R. E., & Brinster, R. L. (1983). Metallothionein-human GH fusion genes stimulate growth of mice. *Science, 222,* 809–814.

Ralph, M. R., Foster, R. G., Davis, F. C., & Menaker, M. (1990). Transplanted suprachiasmatic nucleus determines circadian period. *Science, 247,* 975–978.

Ralph, M. R., & Lehman, M. N. (1991). Transplantation: A new tool in the analysis of the mammalian hypothalamic circadian pacemaker. *Trends in Neurosciences, 14,* 362–366.

Richter, C. P. (1965). *Biological clocks in medicine and psychiatry.* Springfield, IL: C. C. Thomas.

Ross, C. A., McInnis, M. G., Margolis, R. L., & Li, S.-H. (1993). Genes with triplet repeats: Candidate mediators of neuropsychiatric disorders. *Trends in Neurosciences, 16,* 254–260.

Shulman, R. G., Blamire, A. M., Rothman, D. L., & McCarthy, G. (1993). Nuclear magnetic resonance imaging and spectroscopy of human brain function. *Proceedings of the National Academy of Sciences, U.S.A., 90,* 3127–3133.

Sibley, C. G., Comstock, J. A., & Ahlquist, J. E. (1990). DNA hybridization evidence of hominoid phylogeny: A reanalysis of the data. *Journal of Molecular Evolution, 30,* 202–236.

Silva, A. J., Paylor, R., Wehner, J. M., & Tonegawa, S. (1992). Impaired spatial learning in alpha-calcium-calmodulin kinase II mutant mice. *Science, 257,* 206–211.

Silva, A. J., Stevens, C. F., Tonegawa, S., & Wang, Y.

(1992). Deficient hippocampal long-term potentiation in alpha-calcium-calmodulin kinase II mutant mice. *Science, 257,* 201–206.

Strumwasser, F. (1958). Long-term recording from single neurons in brain of unrestrained mammals. *Science, 172,* 469–470.

Strumwasser, F. (1973). Neural and humoral factors in the temporal organization of behavior (The 17th Bowditch lecture). *The Physiologist, 16,* 9–42.

Strumwasser, F. (1987). Circadian oscillators in mollusks and other organisms: Mechanisms and relevance for neuropsychiatry (Swammerdam lecture). In H. H. Boer, W. P. M. Geraerts, & J. Joosse (Eds.), *Neurobiology, molluscan models* (pp. 298–310). Amsterdam: North Holland.

Strumwasser, F. (1988). The bag cell neuroendocrine system of *Aplysia.* In D. Ganten & D. Pfaff (Eds.), *Current topics in neuroendocrinology: Stimulus-secretion coupling as applied to neuroendocrine systems* (pp. 105–122). Heidelberg: Springer-Verlag.

Strumwasser, F., & Vogel, J. M. (1992). Cellular oscillators and biological timing: The role of proteins and Ca^{2+}. *Progress in Brain Research, 92,* 309–320.

Sugamori, K. S., Sunahara, R. K., Guan, H.-C., Bulloch, A. G. M., Tensen, C. P., Seeman, P., Niznik, H. B., & Van Tol, H. H. M. (1993). Serotonin receptor cDNA cloned from *Lymnaea stagnalis. Proceedings of the National Academy of Sciences, U.S.A., 90,* 11–15.

Sutherland, E. W., & Rall, T. W. (1957). The properties of an adenine ribonucleotide produced with cellular particles, ATP, Mg^{++}, and epinephrine or glucagon. *Journal of the American Chemical Society, 79,* 3608.

Tiberi, M., Jarvie, K. R., Silvia, C., Falardeau, P., Gingrich, J. A., Godinot, N., Bertrand, L., Yang-Feng, T. L., Fremeau, R. T., Jr., & Caron, M. G. (1991). Cloning, molecular characterization, and chromosomal assignment of a gene encoding a second D1 dopamine receptor subtype: Differential expression pattern in rat brain compared with the D1A receptor. *Proceedings of the National Academy of Sciences, U.S.A., 88,* 7491–7495.

Usdin, T. B., Mezey, E., Chen, C., Brownstein, M. J., & Hoffman, B. J. (1991). Cloning of the cocaine-sensitive bovine dopamine transporter. *Proceedings of the National Academy of Sciences, U.S.A., 88,* 11168–11171.

Wahlestedt, C., Pich, E. M., Koob, G. F., Yee, F., & Heilig, M. (1993). Modulation of anxiety and neuropeptide Y-Y1 receptors by antisense oligodeoxynucleotides. *Science, 259,* 528–531.

Walsh, C., & Cepko, C. L. (1992). Widespread dispersion of neuronal clones across functional regions of the cerebral cortex. *Science, 255,* 434–440.

Walsh, C., & Cepko, C. L. (1993). Clonal dispersion in proliferative layers of developing cerebral cortex. *Nature, 362,* 632–635.

Wehr, T. A., Sack, D., Rosenthal, N., Duncan, W., & Gillin, J. C. (1983). Circadian rhythm disturbances in manic depressive illness. *Federation Proceedings, 42,* 2809–2814.

Wilson, M. A., & McNaughton, B. L. (1993). Dynamics of the hippocampal ensemble code for space. *Science, 261,* 1055–1058.

Wollum, J. C., & Strumwasser, F. (1983). Is the period of the circadian oscillator in the eye of *Aplysia* directly homeostatically regulated? *Journal of Comparative Physiology, 151,* 253–259.

Woodruff, P. W., Pearlson, G. D., Geer, M. J., Barta, P. E., & Chilcoat, H. D. A. (1993). A computerized magnetic resonance imaging study of corpus callosum morphology in schizophrenia. *Psychological Medicine, 23,* 45–56.

Wu, J.-Y., Tsau, Y., Hopp, H.-P., Cohen, L. B., Tang, A. C., & Falk, C. X. (in press). Consistency in nervous systems: Trial-to-trial and animal-to-animal variations in the responses to repeated applications of a sensory stimulus in *Aplysia. Journal of Neuroscience.*

Zimmerman, N. H., & Menaker, M. (1979). The pineal gland: A pacemaker within the circadian system of the house sparrow. *Proceedings of the National Academy of Sciences, U.S.A., 76,* 999–1003.